patients with a Burkitt's signature, those who were treated with CHOP-like regimens had shorter survival than those who received intensive chemotherapy, but the number of patients was small, and age and stage were not discussed. Hummel et al. found that a c-*myc* rearrangement in the tumors of patients without the Burkitt's signature was an important predictor of a poor outcome.

What are the immediate implications of these studies for clinical practice? RNA extraction and microarray analysis are laborious and expensive and are therefore not ready for real-time diagnosis in clinical practice, but other tools that are currently available to pathologists can be used to identify some of the distinguishing features of cases with the molecular signature of Burkitt's lymphoma (Table 1). Both the gene-expression signature[1] and the immunophenotype[2] of lymphomas with the Burkitt's signature reflect the germinal-center stage of B-cell differentiation. Markers of germinal-center and non–germinal-center B cells can be detected by routine immunohistochemical analysis. *IGH*, *IGL*, *myc*, *BCL2*, and *BCL6* rearrangements can be detected by FISH in paraffin sections. The findings of Dave et al. also suggest new markers that could be used in practice: down-regulation of class I HLA antigens and CD44 and up-regulation of TCL1 in Burkitt's lymphoma; other immunophenotypic markers have been suggested recently as well.[12-15]

In summary, the studies by Dave et al. and Hummel et al. give us another example of the usefulness of gene-array analysis for defining biologic entities with important implications for clinical research and practice. The genes identified may be useful for diagnosis with the use of FISH, real-time polymerase chain reaction, or immunologic methods — and ultimately, for the development of targeted therapies.

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ACE Inhibitors and Congenital Anomalies

J.M. Friedman, M.D., Ph.D.

Angiotensin-converting–enzyme (ACE) inhibitors are among the most widely prescribed antihypertensive agents in the United States, but when used in the second half of pregnancy, they can cause oligohydramnios, fetal growth retardation, pulmonary hypoplasia, joint contractures, hypocalvaria and neonatal renal failure, hypotension, and death.[1-3] These effects result from blockade

of the conversion of angiotensin I to angiotensin II in the developing fetal kidneys.[3] A strikingly similar pattern of fetal anomalies has been reported after treatment of women in the second or third trimester of pregnancy with angiotensin II–receptor antagonists,[1,4] drugs that block the fetal renin–angiotensin system at a different point.

In contrast, fetopathy has not been reported among women who took ACE inhibitors only during the first trimester of pregnancy. This observation has been interpreted to mean that maternal use of ACE inhibitors early in pregnancy does not pose a substantial risk to the developing embryo, although there actually has been very little information available to address this question.

The study reported by Cooper et al. in this issue of the *Journal*[5] is, therefore, of great interest. By linking Tennessee Medicaid records of filled prescriptions and medical records of pregnant women to their infants' medical and vital records, these investigators assessed the risk of major congenital anomalies among 209 children whose mothers were prescribed ACE inhibitors during the first trimester (but not later in pregnancy), as compared with 29,096 unexposed children. Eighteen (8.6 percent) of the exposed infants had major congenital anomalies, a rate that was 2.7 times the rate among unexposed infants, after adjustment for potential confounders. The excess was largely attributable to cardiovascular and central nervous system malformations.

This was an exploratory study, because there was no reason to suspect that any particular congenital anomaly would be more frequent among the children of women treated with ACE inhibitors early in pregnancy. Studies in animals have not suggested that malformations are likely to result from such treatment,[2] and no mechanism by which ACE inhibitors might interfere with embryogenesis is known. Clearly, more research on the teratogenic potential of ACE inhibitors in early pregnancy is needed. This is not the last word on the subject, but it is shocking to realize that it is almost the first.

Captopril, the prototypical ACE inhibitor, was approved by the Food and Drug Administration (FDA) 25 years ago and is one of the most successful drugs ever marketed. Nevertheless, very few data are available on its teratogenic potential in humans. Although a few case reports and small case series have been published, to my knowledge the only epidemiologic study that addresses captopril specifically is an unpublished analysis of Michigan Medicaid data,[6] in which major congenital anomalies were reported in 4 (4.7 percent) of 86 infants of women who had received prescriptions for captopril during the first trimester of pregnancy; the expected rate was 3.5 percent. The situation is similar for the 10 other drugs of this class that are currently available in the United States, despite the fact that some 42 million prescriptions are written for ACE inhibitors each year.[7]

Almost no data are available regarding possible teratogenic risks in humans at the time when most new drugs receive FDA approval, and neither clinical studies nor active surveillance for teratogenic effects is usually required after a drug has been approved. Sponsors must report possible teratogenic effects in drug experience reports, but this voluntary system is a notoriously inefficient and often misleading method of identifying such effects.

Nevertheless, drugs are often prescribed for pregnant women. Medical treatment of chronic conditions such as hypertension may be necessary for affected women to continue their pregnancies safely. In other instances, women may become ill during pregnancy and require drug treatment. Embryonic exposure may also occur when a woman taking medication inadvertently becomes pregnant. More than 10 percent of girls and women between the ages of 15 and 44 become pregnant each year,[8] and almost half of these pregnancies are unintended.[9]

Physicians must weigh the risks and benefits for both the mother and the fetus before prescribing a drug for a pregnant patient. A proper risk–benefit evaluation cannot be performed when the risks to the fetus are unknown, as they are for more than 90 percent of the prescription drugs approved in the United States between 1980 and 2000.[10]

The study by Cooper et al. raises the possibility that maternal ACE-inhibitor treatment early in pregnancy may sometimes cause birth defects. Further study is needed to determine the precise risk and its relationship to individual drugs, but the increase appears to be great enough to require discussion with all women of reproductive age who are prescribed ACE inhibitors. Detailed fetal ultrasonography and echocardiography at about 18 weeks of gestation should be offered to women who have taken such drugs during the

first trimester of pregnancy. A woman who learns that she is pregnant while taking an ACE inhibitor should immediately be switched to another antihypertensive agent to minimize the risk of fetopathy. If we knew that a particular ACE inhibitor posed a teratogenic risk and that other effective antihypertensive agents did not, physicians could avoid the use of the potentially teratogenic drug in women of reproductive age, and especially in those who were planning to become pregnant. Unfortunately, however, insufficient data are available to determine the teratogenic risk for 39 of the 47 other oral antihypertensive drugs[11] listed in the "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure."[12] Therapeutic doses of eight drugs (chlorothiazide, chlorthalidone, hydrochlorothiazide, atenolol, acebutolol, pindolol, nifedipine, and reserpine) are considered unlikely to pose a substantial teratogenic risk,[11] but each drug raises concerns of other kinds. Moreover, the data available on teratogenicity are no better than fair for any of these agents.

Not knowing the teratogenic risks of these drugs really does matter. Because of our ignorance, some pregnant women may not receive treatments that would benefit their own health and that of the fetus. Other women may choose to terminate a pregnancy to avoid the anxiety associated with an undetermined risk. Birth defects caused by teratogenic treatments are preventable, and babies and their mothers are being harmed unnecessarily because we do not know enough about which treatments to use and which to avoid.

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Cholera — Still Teaching Hard Lessons

Richard L. Guerrant, M.D.

At first glance, the report by Saha et al.[1] in this issue of the *Journal* demonstrates the important finding that a single dose of azithromycin is effective in the treatment of cholera in adults. The study reported that within 48 hours after being treated with azithromycin, 73 percent of patients had a cessation of watery diarrhea, as compared with 27 percent of patients who received ciprofloxacin (a drug previously shown to be effective for cholera in adults), and 78 percent had a bacteriologic cure, as compared with only 10 percent of patients who received ciprofloxacin.

Indeed, this dramatic reduction in diarrhea is important since it reduced fluid losses by nearly two thirds, not to mention reducing the need for costly hospitalization and rehydration fluids and decreasing the duration of illness from more than 3 days to a median of only 30 hours. If given early, such an inexpensive single-dose treatment (costing under $1) might further lessen the ef-